REMARKS

In the Action, claims 1-34 are rejected. In response, claims 1 and 10 are amended and claims 2, 3, 11 and 12 are cancelled. The pending claims in this application are claims 1, 4-10 and 13-34, with claims 1, 10 and 23 being independent. In view of these amendments and the following comments, reconsideration and allowance are requested.

Claims 1 and 10 are amended to recite that the cells in the target site are heated to a temperature of at least 42°C. Claim 1 now includes the subject matter of original claims 2 and 3 and claim 10 includes the subject matter of claims 11 and 12. Accordingly, these amendments do not introduce new issues after the final rejection.

Rejection Under 35 U.S.C. § 102(b)

Claims 1, 3, 8, 9, 10, 12, 18 and 19 are rejected as being anticipated under 35 U.S.C. § 102(b) over U.S. Patent No. 5,935,942 to Zeimer. The rejection is based on the position that Zeimer discloses methods and materials for chemically treating a target site using fluorescent dyes that are encapsulated in liposomes where the dyes are released at 41°C, and thus, allegedly anticipates the claims.

It is well settled that anticipation of a claim requires that each and every limitation of the claim be found in a single prior art reference. The Action refers generally to two and a half pages of the Zeimer patent, but has not identified each of the claim limitations in the Zeimer patent. Therefore, the Action has not established anticipation of the claims.

On page 8 of the Office Action, the Examiner asserts that the art, and more specifically Zeimer, teach the concept of treating tissue "utilizing a similar procedure as instantly claimed". Anticipation under 35 U.S.C. § 102(b) requires that each claim element

be found expressly or inherently in the cited art. A "similar procedure" cannot support an anticipation rejection.

The present invention is directed to a method of hyperthermally treating tissue at a temperature that causes cell damage and kills at least some of the cells in the tissue of the target site without denaturing the proteins. Claim 1 as amended is specifically directed to a method of hyperthermally treating tissue by introducing a heat sensitive liposome containing a fluorescent dye where the dye is released at a temperature of at least 42°C and applying a heat source to the target site "to hyperthermally treat the tissue" at a temperature of at least 42°C and to release the dye. Claim 1 further recites the step of fluorescing and visualizing the dye, thereby providing an indicator that a tissue temperature of at least 42°C has been attained that is sufficient to hyperthermally treat the tissue and kill cells in the tissue. Zeimer clearly fails to disclose each of these claimed steps.

As recognized in the Action, Zeimer discloses only "non-invasively" heating to a temperature of 41°C without causing substantial damage to the vasculature. It is known by those skilled in the art that heating tissue to 41°C as in Zeimer does not kill the cells and has little or no affect on the tissue cells. Thus, Zeimer specifically selects 41°C as the upper limit to avoid thermal damage to the tissue cells. Zeimer does not disclose heating tissue to a temperature of at least 42°C as now claimed and does not disclose hyperthermally treating tissue to kill cells without causing protein denaturization. The claimed temperature of at least 42°C causes cell damage and kills the cells in the tissue that are heated to 42°C and above. In contrast, Zeimer does not heat cells or the tissue to a temperature of at least 42°C.

Zeimer also fails to disclose a method of using liposomes that release fluorescent dye at a temperature of at least 42°C. As recognized in the Action, Zeimer discloses heating the blood vessels to 41°C but does not disclose or suggest a heat sensitive liposome that releases

a fluorescent dye at a temperature of at least 42°C. Furthermore, since Zeimer expressly limits the temperature to a minimum of 41°C, one skilled in the art would not consider it obvious to use a liposome that will release its contents only at a temperature above the treatment temperature.

Claim 1 specifically recites "hyperthermally heating" the tissue to kill the cells in the target site without denaturing the proteins. In column 7, line 46, Zeimer defines the term "non-invasively heating" to mean "heating without causing substantial damage to tissue" (emphasis added). Thus, Zeimer clearly fails to disclose heating to kill the cells in the target site as recited in claim 1.

In view of the deficiencies of Zeimer, claim 1 as amended is not anticipated under 35 U.S.C. § 102(b).

As noted in the Action, Zeimer is directed to a method for chemically treating a target site. Zeimer does not hyperthermally treat the tissue. Zeimer uses the liposomes as a carrier for the chemical treating agent, which is released in the target site so that the chemical treating agent is able to chemically treat the target site. The temperature of the treatment of Zeimer is selected to release the chemical treating agent "without causing substantial damage to tissue" (emphasis added). Furthermore, Zeimer does not disclose heating the target site to hyperthermally treat the target site for a time sufficient to kill cells in the tissue. The temperature of Zeimer is clearly below a temperature that causes cell damage. Therefore, Zeimer does not disclose or suggest these features of claim 1.

A review of Zeimer as a whole clearly demonstrates that the process of Zeimer avoids heating that will cause substantial thermal damage. The Action refers to column 6, lines 16-18, as allegedly disclosing heating to cause damage. This passage is taken out of context of the Zeimer disclosure and does not support the contention presented in the Action. This

passage does not disclose that the process of Zeimer actually causes thermal damage or that Zeimer intends to cause thermal damage. Instead, Zeimer only recognized that a laser can cause tissue damage. A cited reference is viewed from the disclosure as a whole. It is improper to isolate one section and read that one section in a vacuum apart from the disclosure as a whole. It appears that the Action contends that some tissue damage occurs notwithstanding Zeimer's definition of "non-evasive heating". Applicant respectfully submits that this position is based on speculation and cannot support an anticipation rejection. Moreover, Zeimer does not disclose a method of heating tissue to at least 42°C to kill cells in the target site as now claimed.

Claim 8 depends from claim 1 to recite that the heat source is a laser, microwave, infrared or ultrasonic source. Claim 9 depends from claim 1 to recite that the heat source is a heated fluid source. The Action refers generally to column 3 through column 7 of Zeimer. The Action has not identified where Zeimer discloses a heated fluid source for heating the target site and it is not seen where Zeimer discloses this step as in claim 9. Accordingly, claims 8 and 9 are not anticipated by Zeimer.

Independent claim 10 as amended is directed to a method of detecting a threshold temperature and hyperthermally treating tissue in an animal. The method as recited in claim 10 introduces a first heat-sensitive liposome containing a first fluorescent dye into the animal to flow through the target site where the fluorescent dye is releasable at a temperature of at least 42°C, and heating the target site to a temperature to release the dye and fluorescing the dye to indicate and visualize a tissue temperature of at least 42°C. Claim 10 further recites the step of continuing heating the target site at a temperature of at least 42°C for a time sufficient to hyperthermally treat the tissue and kill cells in the tissue and at a temperature below the protein denaturization temperature.

Zeimer does not disclose or suggest heating tissue or liposomes at a temperature of at least 42°C to release a fluorescent dye from the liposomes to indicate that a temperature of the tissue in the target site has reached 42°C as recited in claim 10. Moreover, Zeimer does not disclose continuing heating the target site at a temperature of at least 42°C for sufficient time to hyperthermally treat the tissue and kill cells in the tissue. Zeimer specifically avoids thermal damage to the tissue and relies solely on the chemical treatment using the chemical agent released from the liposomes. The temperature of Zeimer is at a temperature that avoids substantial tissue damage and does not kill cells in the tissue as recited in claim 10. Since Zeimer does not disclose hyperthermally treating the tissue, heating the tissue for sufficient time to kill cells in the tissue or releasing the fluorescent dye as an indicator that a minimum temperature is attained to hyperthermally treat the tissue, claim 10 is not anticipated by Zeimer.

Claims 18 and 19 correspond to claims 8 and 9 except for depending from independent claim 10. For the reasons discussed in connection with claims 8 and 9, claims 18 and 19 are also not anticipated by Zeimer.

In view of the above comments, claims 1, 8, 9, 10, 18 and 19 are not anticipated by Zeimer.

Rejection Under 35 U.S.C. § 103(a)

Claims 2, 4-7, 11, 13-17 and 20-34 are rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,935,942 to Zeimer in view of U.S. Patent No. 5,976,502 to Khoobehi et al. Zeimer is cited as in the previous rejection as disclosing a method for chemically treating a target site using fluorescent dyes and tissue reactor substances without causing thermal damage to the tissue. Zeimer is further cited for disclosing the step of

coadministering a fluorescent dye and a tissue reactive agent. The Action incorrectly contends that Zeimer is deficient only in failing to disclose first and second fluorescent dyes enclosed in liposomes.

Khoobehi et al. is not relevant to the claimed invention and is not relevant to Zeimer. Khoobehi et al. is directed to fluorescing and visualizing particles such as liposomes in the blood vessels. Khoobehi et al. avoids releasing the dye and rupturing the liposomes as in the claimed invention. Khoobehi et al. specifically avoids rupturing the liposomes so that the liposomes can be visualized while intact. Khoobehi et al. is directed to a method of detecting blood flow in the retina and choroid, and is not concerned with chemical or thermal treatment to treat or kill cells in the target site.

Khoobehi et al. is cited for disclosing a method of observing blood flow through the eye by injecting liposomes and blood cells containing the dye into the blood stream which can contain a single dye or a mixture of different dyes. The Action contends that it would be obvious to one of ordinary skill in the art to use either a single fluorescent dye or a mixture of different fluorescent dyes as disclosed in Khoobehi et al. within the methods of Zeimer.

Khoobehi et al. does not provide the deficiencies of Zeimer such that the combination of Zeimer and Khoobehi et al. does not render the claims obvious. As noted above, Zeimer is directed to a method of chemically treating tissue in a non-invasive manner. Zeimer specifically applies the laser to the target site in a manner to prevent tissue damage. As disclosed in column 7, lines 58-65 of Zeimer, the non-invasive heating releases the contents of the liposomes "without causing substantial damage to the vasculature or extra vascular interstitial tissue". Therefore, Zeimer does not disclose the basic concept of the claimed invention of heating the tissue to at least 42°C and for a time sufficient to hyperthermally treat the tissue and kill cells in the tissue. Khoobehi et al. clearly fails to disclose

hyperthermally treating tissue. Therefore, the combination of Khoobehi et al. with Zeimer does not render the claims obvious.

Claim 1, which now incorporates the subject matter of claim 2, specifically recites that the fluorescent dye is releasable from the liposome at a temperature of at least 42°C. The Action contends that the temperature is an obvious matter of choice and could be determined through routine manipulative experimentation. This contention is clearly incorrect and contrary to the present record. As disclosed on page 10, paragraph 32 of the specification, heating the tissue to a temperature of at least 42°C ensures that a sufficient temperature is obtained to thermally treat the tissue. It is known in the art that a temperature of 42°C causes extensive cell damage. Zeimer specifically heats the liposomes at a temperature of 41°C to avoid damaging the tissue. The claimed invention is specifically directed to a method of thermally killing cells. Zeimer is specifically directed to a method of releasing the chemical treating agent without causing extensive thermal damage. Zeimer intentionally selects 41°C as the maximum temperature to avoid extensive thermal damage. Heating above 41°C as suggested by the Examiner is contrary to the express teachings of Zeimer and produces a result that is expressly avoided by Zeimer, namely, excessive thermal damage and killing of cells. It is not obvious to one of ordinary skill in the art to increase the temperature of Zeimer. The Action is incorrect in stating that heating the tissue to a temperature of at least 42°C is an obvious matter of design choice in view of Zeimer. Zeimer effectively teaches away from heating the tissue to a temperature of at least 42°C and clearly provides no motivation or incentive to do so. Moreover, Zeimer specifically teaches avoiding excessive thermal treatment. Therefore, claim 1 is not obvious over Zeimer either alone or in combination with Khoobehi et al.

Claims 4 and 5 also depend from claim 1 and recite the step of heating the liposomes to release and activate the bioactive compound at a temperature of at least 42°C. Claims 6 and 7 depend from claim 4 to recite the specific bioactive compound. For the reasons discussed above, Zeimer clearly fails to disclose or suggest heating the tissue and the liposomes to a temperature of at least 42°C since this will kill the cells and cause excessive thermal damage. Since heating the tissue to a temperature of 42°C is known to cause tissue damage, it is not obvious to one of ordinary skill in the art to modify Zeimer in a manner that is specifically contrary to the teachings and intent of Zeimer. Furthermore, Zeimer discloses using agents that are activated by the wavelength of a laser where the "wavelength... does not itself cause substantial damage to tissue". See, for example, column 9, lines 3-6 of Zeimer. Accordingly, claims 4-7 are not obvious over Zeimer either alone or in combination with Khoobehi et al.

Claim 10 includes the subject matter of claim 11 and specifically recites heating the target site to a temperature of at least 42°C. As discussed above, heating tissue to a temperature of 42°C is known to cause tissue damage. Since Zeimer and Khoobehi et al. are specifically directed to methods that prevent excessive thermal damage, it is not obvious to one of ordinary skill in the art to modify Zeimer as suggested in the Action. It is not an obvious matter of choice to modify Zeimer in a manner contrary to the specific teachings of Zeimer and the secondary reference.

Claims 14-17 depend directly or indirectly from claim 10 and are allowable for reciting additional features of the invention that are not disclosed in the art of record. It is also not obvious to one of ordinary skill in the art to modify Zeimer to heat the target site to a temperature range of 42°C to 50°C for one to 10 minutes as in claim 13 to hyperthermally treat the tissue without causing denaturization of the proteins in the tissue, the bioactive

compounds of claims 14-16 or the heat source of claims 18 and 19 in combination with the method of claim 10. Accordingly, claims 14-19 are also not obvious over Zeimer either standing alone or in combination with Khoobehi et al.

Claim 20 depends from claim 10 to recite the step of introducing a second encapsulated fluorescent dye where the dye is releasable from the liposome at a temperature of at least 50°C. Claim 20 further recites the step of visualizing and detecting the second fluorescent dye that is released from the second liposomes and "reducing said temperature of said tissue to a temperature below 50°C" in response to the detected second dye (emphasis added). The invention recited in claim 20 is specifically directed to providing a visual indicator in the form of the second dye when a temperature that causes protein denaturization of the tissue has been attained. Claim 20 also specifically recites the step of reducing the temperature in response to the indication of the second dye, thereby reducing the temperature below the protein denaturization temperature. Thus, the invention of claim 20 provides a first dye to provide an indication that the temperature sufficient for hyperthermally treating the tissue has been attained while also providing an indicator that the temperature is below the protein denaturization temperature. The combination of the first and second dyes provide an indication that the temperature of the tissue is maintained within a specific temperature range. Zeimer, either alone or in combination with Khoobehi et al., do not suggest the claimed method of maintaining the temperature within a specific temperature range.

Claim 21 depends from claim 20 to recite that the cited fluorescent dye is released at a temperature where a protein denaturization occurs and the step of reducing the temperature of the tissue below the protein denaturization temperature in response to the second dye being detected. Khoobehi et al. clearly fails to disclose the use of the second dye that is released at a temperature where protein denaturization occurs and reducing the temperature of the tissue

below the protein denaturization temperature. Claim 22 depends from claim 20 and also recites the step of heating the target site to a temperature below the protein denaturization temperature and below the release temperature of the second fluorescent dye. Zeimer and Khoobehi et al. clearly fail to disclose heating the tissue to a temperature below the release temperature of a dye encapsulated in a liposome. Accordingly, claims 21 and 22 are not obvious over the combination of Zeimer and Khoobehi et al.

Independent claim 23 recites a method of hyperthermally treating tissue by heating the tissue to at least 42°C. Claim 23 also recites introducing first liposomes that release a first fluorescent dye at 42°C and second liposomes containing a second dye that is released at a temperature of at least 50°C. The target site is heated to at least 42°C to release the dye so that the dye fluoresces thereby indicating that a temperature of at least 42°C is attained. Claim 23 further recites that the tissue is heated without releasing the second dye. This provides a visual indicator that a tissue temperature of at least 42°C is attained to effectively hyperthermally treat and kill cells in the target site below 50°C as indicated by the failure to rupture the second liposomes. Thus, the second liposomes serve as an indication that an excess temperature is attained that can cause protein denaturization. By not releasing the second dye from the second liposomes, the second dye does not fluoresce, thereby indicating that the tissue temperature is less than 50°C.

Zeimer and Khoobehi et al. do not disclose or suggest introducing a liposome that releases the dye at 42°C or heating the tissue to at least 42°C. Zeimer and Khoobehi et al. further fail to introduce a second liposome that releases the dye at a temperature of at least 50°C where the second liposome is not ruptured and the second dye is not fluoresced as in claim 23.

Khoobehi et al. discloses the use of two liposomes containing different dyes for an entirely different purpose and for an entirely different method. Khoobehi et al. introduces two different dyes that fluoresce at different wavelengths to selectively visualize the intact liposomes in either the retina or choroid. As disclosed in column 3, line 60 to column 4, line 9, the retina is transparent to the blue-green spectrum while the choroid is impermeable to the blue-green spectrum. Thus, the dyes of Khoobehi et al. are selected so that the liposomes can be observed in the retina without fluorescing the dye in the choroid. The liposomes in Khoobehi et al. are not intended to be released from the liposomes at any time and the laser of Khoobehi et al. does not heat the liposomes to a temperature at which the dyes are released. Khoobehi et al. does not disclose two liposomes that release their respective dye at two different temperatures and does not disclose heating tissue to 42°C. Moreover, Khoobehi et al. fails to disclose or suggest releasing the dye from the first liposome without releasing the dye from the second liposome. Thus, Khoobehi et al. clearly fails to satisfy the deficiencies of Zeimer.

In view of the above, Zeimer and Khoobehi et al. either standing alone or in combination do not disclose heating tissue to at least 42°C, hyperthermally treating to kill cells in the target site without denaturing the proteins, releasing a first dye at a temperature of at least 42°C or treating the target site without releasing the dye from the second liposome.

Claim 24 depends from claim 23 to recite the step of detecting the second fluorescent dye and reducing the temperature of the tissue below the protein denaturization temperature of the tissue. Zeimer and Khoobehi et al. clearly fail to disclose or suggest reducing the temperature of the tissue in response to the detection of a dye. Accordingly, claim 24 is not obvious over the combination of Zeimer and Khoobehi et al.

Claims 25-34 are also allowable as depending from an allowable base claim and for reciting additional features that are not disclosed or suggested in the art of record. For example, the cited art does not disclose the use of different colored dyes as in claim 25, the phospholipids of claims 26 and 27, or the specific bioactive compounds of claims 28-31, either alone or in combination with the features of claim 23. Accordingly, these claims are not obvious over the art of record.

Claim 32 depends from claim 23 to recite that the first liposomes release the dye at a temperature of about 42-50°C. Thus, claim 32 recites the use of liposomes that rupture and release the dye in a temperature range that is effective for hyperthermally treating the tissue without causing protein denaturization. Zeimer and Khoobehi et al. do not disclose or suggest a liposome that ruptures at a temperature above the minimum temperature required for hyperthermal treatment and below the protein denaturization temperature. Claim 33 depends from claim 23 to recite that the first liposomes rupture and release the dye at a temperature of about 45°C to about 49°C. As noted above, tissue damage occurs at temperatures above 42°C and Zeimer and Khoobehi et al. specifically select liposomes that rupture below the temperature at which cell damage begins to occur. Zeimer and Khoobehi et al. provide no motivation or incentive to use a liposome that ruptures at a temperature of 45°C which is at a temperature that will cause tissue damage. Claim 34 depends from claim 23 to recite that the second liposomes rupture and release the dye at a temperature of about 50°C to 60°C. This temperature is well above the temperature at which tissue damage occurs and is above the temperature in which protein denaturization occurs. Zeimer and Khoobehi et al. provide no motivation of using a liposome that ruptures above the protein denaturization temperature. Accordingly, claims 32-34 are not obvious over the combination of Zeimer and Khoobehi et al.

In view of the deficiencies of Zeimer and Khoobehi et al., claims 1-34 are not anticipated by or obvious over Zeimer, either alone or in combination with Khoobehi et al. Accordingly, reconsideration and allowance are requested.

Respectfully submitted,

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